PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Applicant's or agent's file reference P2772PCT-GN	Date of mailing (*day/month/year*) FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/JP2004/017274	19.11.2004	21.11.2003

International Patent Classification (IPC) or both national classification and IPC

Applicant
DAIICHI ASUBIO PHARMA CO.,LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/JP	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/237 (cover sheet) (January 2004)

WRITTEN OPINION OF THE
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Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language: _____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☒ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☒ in computer readable form

c. time of filing/furnishing

☐ contained in the international application as filed.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 1, 3-16, 32, 33 (partial)

because:

☒ the said international application, or the said claims Nos. 1, 3-16, 32, 33 (partial) relate to the following subject matter which does not require an international preliminary examination (*specify*):

Claims 1 and 3-16 describe methods for growing myocardial cells including a step of transducing certain nucleic acid into myocardial cells of an organism and claims 32 and 33 methods for curing heart diseases. These include methods for treatment of the human body by surgery or therapy as well as diagnostic methods, which does not require an international preliminary examination.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 1, 3-16, 32, 33 (partial)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-33	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-33	NO
Industrial applicability (IA)	Claims	1-33	YES
	Claims		NO

2. Citations and explanations:

Document 1: Circ Res., Jan. 2003, Vol. 92, No. 1, e12-9.
Document 2: Circ Res., 1999, Vol. 85, No. 2, p. 117-27.
Document 3: Biochem Biophys Res Commun., 2002, Vol. 296, No. 5, p. 1372-7.
Document 4: Cell, 1994, Vol. 78, No. 1, p. 67-74.
Document 5: Curr Biol., 1999, Vol. 9, No. 12, p. 661-4.

Document 1 describes a method for increasing the number of myocardial cells by transducing a gene encoding cycline D1 and a gene encoding CDK4 into myocardial cells.
Document 2 describes a method for increasing the number of myocardial cells by deleting p27KIP1.
Document 3 describes a method for knocking targeted gene out by employing siRNA .
Document 4 describes that p27 inhibits cycline D1-cdk4 family.
Document 5 describes that SCFSKp2 complex splits p27KIP1.

The inventions of claims 1-8, 13-21 and 26-33 do not appear to involve an inventive step on account of documents 1-3.
As it is recognized to have been well-known that cycline D1, CDK4 and p27KIP1 regulate growth of cells by mutual reaction, a person skilled in the art could have easily conceived to apply a technology for increasing the number of myocardial cells by deleting p27KIP1 described in document 2 to a technology for increasing the number of myocardial cells described in document 1, and in doing so, to employ the siRNA method which is a well-known technology (see document 3 etc., if necessary).

The inventions of claims 1-12, 15-25 and 28-33 do not appear to involve an inventive step on account of documents 1, 2, 4 and 5.
A person skilled in the art could have easily conceived to use a gene encoding skp2 which is shown to have a function of splitting p27KIP1 in documents 4 and 5, when further to apply a technology for increasing the number of myocardial cells by deleting p27KIP1 described in document 2 to a technology for increasing the number of myocardial cells described in document 1.

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims as a whole cannot be said to be sufficiently supported by specifications or disclosed fully, as only cycline D1, CDK4 and p27 are disclosed as embodiments of "cycline", "cyclin-dependent kinase" and "Cipf/Kip family proteins", respectively.